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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,754	07/06/2001	Keith D. Allen	R-372	4570

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EXAMINER
PAPPU, SITA S

ART UNIT	PAPER NUMBER
1636	8

DATE MAILED: 05/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/900,754	ALLEN ET AL.	
	Examiner	Art Unit	
	Sita Pappu	1636	

-- The MAILING DATE of this c mmunication appears n the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *16 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Currently, claims 1-23 are pending in the instant application. This Office Action is in response to the communication filed by the Applicant in paper #7 on 03/08/2002.

Election/Restrictions

Applicant's election, with traverse, of Group I, claims 1-15, 17-22, is acknowledged. Applicant traversed on the grounds that the Invention of Group II is related to the Invention of Group I and that a search can be performed without a serious burden to the examiner. Applicant's arguments are fully considered, but are not found persuasive. The agent of Group II is distinct from the targeting construct, the KO mouse and the methods of making the KO mouse and using the KO mouse in a method of identifying an agent having an effect on a phenotype. Thus, the original restriction is still deemed proper and is therefore, made FINAL. Accordingly, claims 16 and 23 are withdrawn from consideration. This paper contains an examination of claims 1-15, 17-22 on their merits.

Priority

Applicant's claim of priority to the provisional applications 60/216,109 (filed 07/06/2000), 60/223172 (filed 08/07/2000), 60/244,111 (filed 10/26/2000) and 60/301,217 (filed 06/26/2001) is acknowledged.

Drawings

Draftsperson objected to the drawings. See attached PTO-948.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-15, 17-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a homozygous knockout mouse comprising a disruption in the mTMT (mouse transmembrane tryptase) gene and exhibiting phenotypic features such as decreased body weight, decreased thymus weight, decreased thymus to body weight ratio, or increased pre-pulse inhibition as compared to wild type mice, a method of producing such a transgenic mouse, and a method of identifying an agent that modulates the expression and/or function of mTMT gene and thereby ameliorates a phenotype associated with the disruption, and a cell derived from the KO mouse, does not reasonably provide enablement for any transgenic and/or knockout animal comprising any disruption in any tryptase gene. Further, the specification is not enabling for a knockout mouse comprising any disruption in any tryptase gene and for any cell comprising any disruption in a tryptase gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided

by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention:

Claims 5-15, 17-22 are drawn to a cell comprising a disruption in a tryptase gene, a non-human transgenic animal comprising a disruption in a tryptase gene, a cell from that transgenic animal, a method of producing the mouse with any disruption in the said gene, and a method of identifying an agent having an effect on a phenotype associated with the transgenic mouse. Thus, the nature of the invention is directed to transgenic animals and methods of using the transgenic animals in identifying agents that modulate gene expression.

Breadth of Claims:

In the instant case, the claims 5-15, 17-22 encompass any transgenic animal containing any disrupted allele for the gene that encodes any tryptase. Further, the claims encompass any knockout mouse comprising any disruption in tryptase gene and exhibiting the phenotypes of decreased body weight, decreased thymus weight, decreased thymus to body weight ratio, or increased pre-pulse inhibition as compared to wild type mice. Further, the claims encompass any cell comprising any disruption in a tryptase gene and encompass all cells capable of undergoing homologous recombination (specification page 3, line 5). The disruption, as disclosed in the specification (page 7, line 6) includes any insertion, deletion or substitution in any

portion of the gene (introns, exons, regulatory regions). The claims, therefore, encompass all such disruptions and also cover animals that exhibit enhanced tryptase activity (page 7, line 13).

The specification does not provide an enabling disclosure for the full scope of transgenic animals of the type claimed. The only embodiment enabled by the specification within the scope of claims 5-15, 17-22 is for a homozygous knockout mouse comprising a disruption in the mTMT gene that results in loss of function of the tryptase and exhibiting phenotypic features such as decreased body weight, decreased thymus weight, decreased thymus to body weight ratio, or increased pre-pulse inhibition as compared to wild type mice, a method of producing such a transgenic mouse, and a method of identifying an agent that modulates the expression of mTMT gene and thereby ameliorates a phenotype associated with the disruption. Thus the breadth of claims is very broad and encompasses any transgenic animal and a knockout mouse with any disruption in any tryptase gene and includes any and all mutant forms, substitutions, deletions, or insertions in any tryptase gene (specification, page 7, paragraph 2).

Amount of guidance in the specification and Working Examples:

The specification discloses the use of a specific mTMT gene in producing a homozygous transgenic, knockout mouse and using the KO mouse to screen for agents that modulate its expression and/or function through the use of known screening methods wherein the knockout mouse exhibits phenotypic changes that include

decreased body weight, decreased thymus weight, decreased thymus to body weight ratio, or increased pre-pulse inhibition as compared to wild type mice.

The specification and the working examples provide sufficient guidance to practice the invention with only a homozygous, knockout mouse containing two disrupted alleles for the gene that encodes a murine TMT gene wherein the disruption results in loss of function of tryptase. The specification does not teach how to make and use the invention with other species of transgenic or knockout animals and with any knockout mouse with any form of disruption in the gene encoding any tryptase, as claimed in the claims 5-15, 17-22. Further, the specification does not teach how to make and use any cell comprising any type of disruption in a tryptase gene as claimed. The scope of claims 5-15, 17-22, thus surpasses that enabled by the specification.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan:

Although the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the claims as specified and use the invention with any and all transgenic animals as claimed. The specification and the working examples provide sufficient guidance to practice the invention with only a homozygous, knockout mouse containing two disrupted alleles for the gene that encodes a mTMT wherein the gene knocked out is a nonfunctional mTMT3 gene. However, neither the specification nor the working examples provide enough guidance on how to practice the invention with any and all

transgenic animals and/or transgenic mice carrying any and all transgene(s) of the types recited in the claims.

When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). The specification discloses the phenotype of a homozygous mTMT knockout mouse comprising a disruption in the mTMT gene and fails to disclose the phenotypes of any and all KO animals with a disruption in any tryptase gene. Thus, the phenotype of any transgenic or knockout animal is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic and/or knock out animals, including mice, that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification. Thus, the specification is enabling for a method of identifying an agent that modulates the phenotype of a KO mouse using only a homozygous KO mouse of the instant invention.

Further, the transgene expression and the physiological consequences of transgene products are not always accurately predicted in transgenic mouse studies (pg.62, paragraph1, lines 7-9 in Wall, R.J. 1996. Theriogenology 45:57-68). Thus, the invention while being enabled for a homozygous knockout mouse containing two disrupted alleles for the gene that encodes a mTMT, does not extend the predictability of the invention to other animal systems.

The particular genetic elements required for expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall, 1996). Therefore, the phenotype of knockout animals is not always predictable. For example, Jacks et al. (1992) describe Rb KO mice that do not display retinoblastoma; rather they exhibit the unexpected phenotype of pituitary tumors. The pituitary tumors arise from cells lacking a wild-type Rb allele. Thus, tumors were found to arise not in retinas, as in humans, but in the pituitary gland (page 299, Discussion, paragraphs 1 and 3). Therefore, in the absence of specific guidance and working examples, the production of transgenic animals with the scope as claimed is unpredictable. In such a situation, one skilled in the art would not know how to make and use the invention as claimed, without undue experimentation.

The specification fails to provide an enabling disclosure for the preparation of other species of knockout animals besides mice having a disruption in the mTMT gene because the guidance offered in the specification is limited to the preparation of mice harboring such mutations and no teachings or guidance are offered in regard to how one would have prepared any other type of animal having the recited gene disruption. Since homologous recombination is required for gene targeting methods such as employed in the instant invention, embryonic stem (ES) cell technology must be available to carry out the method. The only species in which such technology was known was the mouse and the artisan did not accept that it was possible to have prepared ES cells in other species (see e.g. Bradley et al., paragraph bridging pages

537-538). Campbell and Wilmut, 1997 acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p. 65). Likewise, Mullins et al. (1996) teach that "[a]lthough to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (p. S38, column 1, paragraph 1. Thus, knockout animals cannot be prepared for any species other than the mouse. Since ES cell technology was required to produce the claimed animals and practice the claimed methods of using such animals, in the absence of such technology available in other species, one skilled in the art would have been required to exercise undue experimentation to produce the claimed animals and to practice of the claimed methods in species other than mice.

In view of the limited guidance in the specification, and limited working examples directed to transgenic, knockout mice with a specific knockout gene and exhibiting a specific phenotype, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to make and use the invention in its full scope as claimed. Thus, the enabled scope of the claims is limited to a homozygous and/or a heterozygous knockout mouse comprising a disruption in the mTMT gene and exhibiting phenotypic features such as decreased body weight, decreased thymus weight, decreased thymus to body weight ratio, or increased pre-

pulse inhibition as compared to wild type mice, a method of producing such a transgenic mouse, and a method of identifying an agent that modulates the expression and/or function of mTMT gene and thereby ameliorates a specific phenotype associated with the said disruption.

Claims 1-5, 8, 9, 11-15, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are referred to the guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, No. 4, pp. 1099-1111 (also available at www.uspto.gov).

The specification does not provide or point to a written description of the genus of tryptase genes recited in the claims. Claims 1-5, 8, 9, 11-15, are directed to a transgenic and/or knockout animal and a cell containing any disruption in any tryptase gene. However, the specification only describes a single species of a transgenic, knockout mouse of the type claimed, wherein the said disruption is within the gene that encodes a specific tryptase, a murine mTMT gene. The specification fails to teach other "tryptase genes" from other species of animals besides mice. In analyzing whether a written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the claims encompass the whole genus of 'tryptase genes' and include any and all transgenic animals that contain any altered allele for the gene that encodes

a tryptase. Thus for the claims to meet the written description requirement, other representative species of "tryptase genes", should be described by their complete structure or by other relevant identifying characteristics, in the specification.

Next, then, it is determined if a representative number of species have been sufficiently described by other relevant identifying characteristics. In the instant case, no identifying characteristics are provided for the genus of tryptase gene disruptions recited in the claims. Thus the limited information in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed genus of tryptase gene disruptions. Further, the specification discloses that no serine protease, which possesses an overall structure that resembles the mTMT, has been discovered (specification, page 2, line 16). Thus, it is concluded that the written description requirement is not satisfied for the claimed genus of "tryptase genes".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12 and 14 are indefinite in their recitation of "function of a tryptase gene". The meaning of this phrase is not clear and as such the metes and bounds of the phrase are not clearly set forth. Clarification is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-15, 17-22, are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (1999, J. Biol. Chem. Vol.274, no. 43, pp.30784-30793) and Smyth et al. (1996, Journal of Leucocyte Biology, vol. 60, no.5, pp.555-562) further in view of Capecchi et al. (1989, TIG, vol. 5, no. 3, pp. 70-76).

Wong et al. teach the nucleotide sequence of the murine (mTMT) and human (hTMT) transmembrane tryptase genes (Fig. 2, page 30786; Figs. 5 and 6, page 30788).

Wong et al. do not teach the use of their polynucleotide sequence to generate KO mice or targeting constructs.

Smyth et al. (1996) teach Granzymes, a family of serine proteases and advocate that the creation of knockout mice deficient in this gene, should elucidate their precise role and biological function. Smyth et al. thus teach that knockout mice are a good model to study the function of tryptases and thereby provide the motivation to generate knockout mice having a disruption in mTMT gene, a transmembrane tryptase. Methods of generating mice deficient in a gene are known in the art at the time of filing, as taught by Capecchi et al. (1989, TIG, vol. 5, no. 3, pp. 70-76).

Therefore it would have been obvious to one of ordinary skill in the art to use the nucleotide sequence of Wong et al. to generate knockout mice and use them as model systems to screen for agents that modulate the function, and expression of mTMT, with a reasonable expectation of success. The motivation to do so was provided by Smyth et al. and the expectation of success was derived from the teachings of Capecchi et al. (1989) who taught that KO mice can be successfully generated by gene targeting techniques.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (8:30 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305 1998. The fax phone

numbers for the organization where this application is assigned are (703) 308 4242 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Tracey Johnson at (703) 305-2982.

S. Pappu
May 3, 2002

Anne-Marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER